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1/22/97 AD

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No. 40399/321/NIHD

In re patent application of

Jeffrey S. RUBIN et al.

Art Unit: 1812

Serial No. 08/477,983

Examiner: Saoud, C.

Filed: June 7, 1995

For: AN EPITHELIAL CELL SPECIFIC GROWTH FACTOR, KERATINOCYTE
GROWTH FACTOR (KGF)

SUBMISSION OF SUBSTITUTE SPECIFICATION

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Applicants submit herewith a Substitute Specification incorporating the amendments to the specification found in applicant's amendment of March 31, 1989 in the parent application, Serial No. 07/304,281, as well as other typographical and ministerial corrections. In accordance with 37 C.F.R. § 1.25 and M.P.E.P. 608.01(q), applicants have added no new matter. Applicants also submit herewith a marked-up copy of the originally filed specification. The Substitute Specification includes the same changes that are indicated in the marked-up copy of the original specification showing additions and deletions.

Respectfully submitted,

Date: January 14, 1997

Patricia D. Granados
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202/672-5300

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of

RUBIN et al.

Group Art Unit: 000

Serial No. 07/304,281

Examiner: Unknown

Filed: January 31, 1989

Title: DNA ENCODING A GROWTH FACTOR SPECIFIC FOR EPITHELIAL
CELLS

* * * * *

March 31, 1989

P R E L I M I N A R Y A M E N D M E N T

Hon. Commissioner of Patents
and Trademarks
Washington, DC 20231

FILE COPY

Sir:

Please amend the above-referenced application as follows:

IN THE CLAIMS:

Claim 4, page 82, line 24: before "vii", insert --and--

Claim 17, page 84, line 17: delete "and"

Claim 17, page 84, line 20: before "iii", insert --and--

IN THE SPECIFICATION:

Page 3, lines 6-7: delete "see reference I-1 in
Experimental Section I, below", insert --James, R. and Bradshaw,
R.A., 1984, *Ann. Rev. Biochem.* 53, 259-292--

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Page 2

Page 3, lines 9-10: delete "reference II-2 in Experimental
Section II, below", insert --Sporn, M. B. and Todaro, G. J.,
1980, *N. Eng. J. Med.* 303, 878-880--

Page 3, line 15: delete "I-1" and insert --Hunter, T. and
Cooper, J.A., 1985, *Annu. Rev. Biochem.* 54, 897-930--

Page 3, line 25: after "hst", insert --, FGF-5--

Page 4, line 16: delete "tissues", insert --cells--

Page 6, line 14: after "hst", insert --, FGF-5--

Page 12, line 1-2: delete "antibodies can be used for
detection or purification of the"

Page 13, line 10: delete "and", insert --an--

Page 15, line 13: delete "a single", insert --the
predominant--

Page 15, line 14: delete "human embryonic lung", insert
--stromal--

Page 15, line 14-15: delete "and from ... no transcript"

Page 15, line 16-18: delete "was detected ...
endothelial cells", and insert --but was not detected in the
epithelial cell lines--

Page 18, line 1: delete "cell target", insert --
target cell--

Page 22, line 21: after "KGF", insert --, FGF-5--

Page 24, line 14: delete "NH₂", insert --N--

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Page 24, line 27: delete "NH₂", insert --N--

Page 24, line 27: delete "about 40", insert --46--

Page 25, line 3: delete "about 140", insert --116--

Page 25, line 4: delete "CO₂-", insert --C--

Page 25, lines 8-9: delete "lacks susceptibility to", insert
--its activity is enhanced by--

Page 30, line 17: delete "45,", insert --45 plus an R at
its C-terminus--

Page 38, line 27-8: delete "University of California",
insert --Lawrence Berkeley Laboratory--

Page 48, line 21: in each of two instances, after ")",
insert --,--

Page 48, line 22: after "factor", insert --(Roberts, R.,
et al., 1988, *Nature* 332, 376-378)--

Page 48, line 23: after "interleukin 3", delete ". (I-25)"
and insert --(Roberts, R., et al., 1988, *Nature* 332, 376-378).--

Page 53, line 21: after "h₂", insert --, FGF-5--

Page 56, line 3: delete "human epithelial"; after "from",
insert --the conditioned medium of human fibroblast--

Page 56, line 5: delete "supernatents"; insert --
supernatants--

Page 56, line 19: delete "bleed", insert --bleeds--

Page 59, lines 13-18: delete entire sentence to end of
at line 18, beginning with "Whereas ..."

Page 61, line 1: after "hst", insert --, FGF-5--

Page 62, line 20: delete "an", insert --in--

Page 64, line 15: delete "arg", insert --Arg--;

delete "asp", insert --Asn--

Page 64, line 17: delete "asp", insert --Asn--

Page 64, line 18-19: delete "appeared to be an arg",
insert --was not identified--

Page 66, line 14: delete "Ph", insert --pH--

Page 67, line 19: delete "Sau3AI", insert --SauI --

Page 67, line 20: delete "GATC", insert --CCTGAGG--

Page 67, line 21: delete "78 and 79 (arg and ile",
insert --76, 77, and 78 (Tyr, Leu and Arg--

Page 67, line 24: delete "39 (arg) and 40", insert --
37 (Phe), 38 (Leu) and 39 (Arg)--

Page 68, line 5: delete "expressions", insert --
expression--

Page 68, line 19: delete "cell target", insert --
target cell--

Page 70, lines 5-9: delete entire sentence beginning
with "The hst gene ...", insert --FGF-5 and hst are transforming
genes originally detected by DNA-mediated gene transfer.--

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Page 5

Page 72, line 3: after "mouse," insert --41% identical to
FGF-5 (human)--

Page 72, line 11: after "KGF", insert --, FGF-5--

Page 80, line 5: delete "are", insert --is--

In each instance of its use, as listed below, delete the
citation "I-1" and insert --James, R. and Bradshaw, R.A., 1984,
Ann. Rev. Biochem. 53, 259-292--:

Page 3: line 13; line 15

Page 4: line 3 (two instances); line 5; line 8; line 16

In each instance of its use, as listed below, delete the
citation "I-2" and insert --Doolittle, R.F., *et al.*, 1983, *Science*
221, 275-277--:

Page 3: line 13

Page 4: line 5; line 16

In each instance of its use, as listed below, delete the
citation "I-3" and insert --Waterfield, M.D., *et al.*, 1983, *Nature*
304, 35-39--:

Page 4: line 17

In each instance of its use, as listed below, delete the
citation "I-5" and insert --Wright, N. and Allison, M., 1984, *The*
Biology of Epithelial Cell Populations [Oxford University Press, New York]
Vol. 1, pp. 3-5--

Page 4: line 14

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Page 6

In each instance of its use, as listed below, delete the citation "I-6" and insert --Weissman, B.E. and Aaronson, S.A., 1983, *Cell* 32, 599-606--

Page 16: line 21; line 25

In each instance of its use, as listed below, delete the citation "I-7" and insert --Falco, J.P., et al., 1988, *Oncogene* 2, 573-578--

Page 17: line 21; line 7

In each instance of its use, as listed below, delete the citation "I-8" and insert --Aaronson, S.A. and Todaro, G.J., 1968, *Virology* 36, 254-261--

Page 19: line 3;

Page 35, line 11

In each instance of its use, as listed below, delete the citation "I-9" and insert --Laemmli, U.K., 1970, *Nature* 227, 680-685--

Page 37: line 23;

In each instance of its use, as listed below, delete the citation "I-10" and insert --Merril, C.R., et al., 1981, *Science* 211, 1437-1438--

Page 37: line 25;

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Page 7

In each instance of its use, as listed below, delete the citation "I-11" and insert --Jainchill, J.L., Aaronson, S.A. and Todaro, G.J., 1969, *J. Virol.* 4, 549-553--

Page 38: line 21;

In each instance of its use, as listed below, delete the citation "I-12" and insert --Caputo, J.L., Hay, R.J. and Williams, C.D., 1979, *In Vitro* 15, 222-223--

Page 38: line 23;

In each instance of its use, as listed below, delete the citation "I-13" and insert --Stampfer, M.R. and Bartley, J.C., 1985, *Proc. Natl. Acad. Sci. USA* 82, 2394-2398--

Page 38: line 26;

In each instance of its use, as listed below, delete the citation "I-14" and insert --Sharefkin, J.B., Fairchild, K.D., Albus, R.A., Cruess, D.F. and Rich, N.M., 1986, *J. Surgical Res.* 41, 463-472--

Page 39: line 6;

In each instance of its use, as listed below, delete the citation "I-15" and insert --Cohen, S., 1962, *J. Biol. Chem.* 237, 1555-1562--

Page 40: line 16;

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Page 8

In each instance of its use, as listed below, delete the citation "I-16" and insert --DeLarco, J.E. and Todaro, G.J., 1978, *Proc. Natl. Acad. Sci. USA* 75, 4001-4005--

Page 40: line 16;

In each instance of its use, as listed below, delete the citation "I-17" and insert --Raines, E.W. and Ross, R., 1982, *J. Biol. Chem.* 257, 5154-5160--

Page 41: lines 6-7;

In each instance of its use, as listed below, delete the citation "I-18" and insert --Shing, Y., Folkman, J., Sullivan, R., Butterfield, C., Murray, J. and Klagsburn, M., 1984, *Science* 223, 1296-1299--

Page 41: lines 6-7;

In each instance of its use, as listed below, delete the citation "I-19" and insert --Gospodarowicz, D., *et al.*, 1984, *Proc. Natl. Acad. Sci. USA* 81, 6963-6967--

Page 4: lines 1-2;

Page 41: lines 6-7;

Page 48: line 21;

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Page 9

In each instance of its use, as listed below, delete the citation "I-20" and insert --Maciag, T., *et al.*, 1984, *Science* 225, 932-935--

Page 4: lines 1-2 (two instances;

Page 41: lines 6-7;

Page 48: line 21;

In each instance of its use, as listed below, delete the citation "I-21" and insert --Conn, G. and Hatcher, V.B. (1984) *Biochem. Biophys. Res. Comm.* 124, 262-268--

Page 4: lines 1-2;

Page 41: lines 6-7;

Page 48: line 21;

In each instance of its use, as listed below, delete the citation "I-22" and insert --Lobb, R.R. and Fett, J.W., 1984, *Biochemistry* 23, 6295-6299--

Page 41: lines 6-7;

Page 48: line 21 (two instances;

In each instance of its use, as listed below, delete the citation "I-23" and insert --Bradford, M., 1976, *Anal. Biochem.* 72, 248-254--

Page 87: line 11;

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Page 10

In each instance of its use, as listed below, delete the citation "I-24" and insert --Lipman, D.J. and Pearson, R.W., 1985, *Science* 227, 1435-1441--

Page 46: line 7;

In each instance of its use, as listed below, delete the citation "I-25" and insert --Roberts, R., et al., 1988, *Nature* 332, 376-378--

Page 4: line 5; line 8; line 11;

Page 48: line 23; line 24; line 27;

Page 49: line 2;

In each instance of its use, as listed below, delete the citation "I-26" and insert --Libermann, T.A., et al., 1987, *EMBO J.*, 6, 1627-1632--

Page 48: line 24;

In each instance of its use, as listed below, delete the citation "I-27" and insert --Shipley, G.D., et al., 1988, *J.Cell Biochem. Supp* 12A, 125, abstr. C420--

Page 48: line 24;

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In each instance of its use, as listed below, delete the citation "I-28" and insert --Vlodavsky, I., *et al.*, 1987, *Proc. Natl. Acad. Sci. USA* 84, 2292-2296--

Page 4: line 11;

Page 48: line 27;

Page 49: line 2;

In each instance of its use, as listed below, delete the citation "I-29" and insert --Gilchrest, B.A., *et al.*, 1983, *J. Cell Physiol.* 117, 2325-240--

Page 49: line 4;

In each instance of its use, as listed below, delete the citation "I-30" and insert --Chan, K.Y. and Haschke, R.H., 1983, *Exp. Eye Res.* 36, 231-246--

Page 49: line 4;

In each instance of its use, as listed below, delete the citation "I-31" and insert --Stiles, A.D., Smith, B.T. and Post, M., 1986, *Exp. Lung Res.* 11, 165-177--

Page 49: line 4;

Page 49, line 17 through page 52, end, delete entire section entitled "REFERENCES FOR EXPERIMENTAL SECTION I".

In each instance of its use, as listed below, delete the citation "II-3" and insert --Rubin, J. S., Osada, H., Finch, P.

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W., Taylor, W. G., Rudikoff, S. and Aaronson, S. A., 1989, *Proc. Natl. Acad. Sci. USA* (in press), February, 1989--

Page 54: line 5;

In each instance of its use, as listed below, delete the citation "II-4" and insert --Crick, F. H. C., 1966, *J. Mol. Biol.* 19, 548-555--

Page 58: line 18;

In each instance of its use, as listed below, delete the citation "II-5" and insert --Ohtsuka, E., Matsuki, S., Ikehara, M., Takashi, Y. and Matsubara, K., 1985, *J. Biol. Chem.* 260, 2605-2608--

Page 58: line 21;

In each instance of its use, as listed below, delete the citation "II-6" and insert --Miki, T., Matsui, T., Heidaran, M. and Aaronson, S. A., unpublished observations--

Page 58: line 23;

In each instance of its use, as listed below, delete the citation "II-7" and insert --Aaronson, S. A. and Todaro, G. J., 1968, *Virology* 36, 254-261--

Page 58: line 25;

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In each instance of its use, as listed below, delete the citation "II-8" and insert --Kozak, M., 1987, *Nucl. Acids Res.* 13, 8125-8148--.

Page 60: line 6;

In each instance of its use, as listed below, delete the citation "II-9" and insert --Lipman, D. J. and Pearson, R. W., 1985, *Science* 227, 1435-1441--

Page 60: line 24;

In each instance of its use, as listed below, delete the citation "II-10" and insert --Thomas, K., 1987, *FASEB J.* 1, 434-440--

Page 70: line 4;

Page 72, line 18;

In each instance of its use, as listed below, delete the citation "II-14" and insert --Jakobovits, A., Shackleford, G. M., Varmus, H. E. and Martin, G. R., 1986, *Proc. Natl. Acad. Sci. USA* 83, 7806-7810--

Page 70: line 10;

In each instance of its use, as listed below, delete the citation "II-15" and insert --Peters, G., Brookes, S. and Dickson, S., 1983, *Cell* 33, 364-377--

Page 70: line 13;

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Page 14

In each instance of its use, as listed below, delete the citation "II-16" and insert --von Heijne, G. (1986) *Nucl. Acids Res.* 14, 4683-4690--

Page 72: line 14;

In each instance of its use, as listed below, delete the citation "II-17" and insert --Moore, R. Casey, G., Brookes, S., Dixon, M., Peters, G. and Dickson, C., 1986, *EMBO J.* 5, 919-924-

Page 72: line 20;

In each instance of its use, as listed below, delete the citation "II-18" and insert --Schwarzbauer, J.E., Tamkum, J.M., Lemischka, I. R. and Hynes, R. O., 1983, *Cell* 35, 421-431--

Page 73: line 4;

In each instance of its use, as listed below, delete the citation "II-19" and insert --Shaw, G. and Kamen, R., 1986, *Cell* 46, 659-667--

Page 73: line 17;

In each instance of its use, as listed below, delete the citation "II-20" and insert --Birnstiel, M. L., Busslinger, M. and Strub, K., 1985, *Cell* 41, 349-359--

Page 73: line 19;

In each instance of its use, as listed below, delete the citation "II-21" and insert --Schrieber, A. B., Kenny, J.,

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Kowalski, W., Friesel, J., Mehlman, T. and Maciag, T., 1985, *Proc Natl. Acad. Sci. USA* 82, 6138-6142--

Page 73: line 26;

In each instance of its use, as listed below, delete the citation "II-22" and insert --Gospodarowicz, O. and Cheng, J., 1986, *J. Cell Physiol.* 128, 475-485--

Page 73: line 27;

In each instance of its use, as listed below, delete the citation "II-23" and insert --Thomas, K. A. and Gimenez-Gallego, G., 1986, *Trends Biochem. Soc.* 11, 81-84--

Page 74: line 13;

In each instance of its use, as listed below, delete the citation "II-24" and insert --Gensburger, C., Labourdette, G. and Sensembrenner, M., 1987, *FEBS Lett.* 217, 1-5--

Page 74: line 14;

In each instance of its use, as listed below, delete the citation "II-25" and insert --Delli-Bovi, P, Curatola, A M., Kern, F. G., Greco, A., Ittman, M. and Basilico, C., 1987, *Cell* 50, 729-737--

Page 74: line 18;

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In each instance of its use, as listed below, delete the citation "II-26" and insert --Sanger, F., Nicklen, S. and Coulson, A. R., 1977, *Proc. Natl. Acad. Sci. USA* 74, 5463 5467--

Page 54: line 20;

In each instance of its use, as listed below, delete the citation "II-27" and insert --Yanisch-Perron, C., Vieira, J. and Messing, J., 1985, *Gene* 33, 103-119--

Page 54: line 22;

In each instance of its use, as listed below, delete the citation "II-28" and insert --Zhan, X., Bates, B., Hu, X. and Goldfarb, M., 1988, *Mol. Cell. Biol.* 8, 3487-3495--

Page 70: line 15;

In each instance of its use, as listed below, delete the citation "II-29" and insert --Abraham J. A., et al., 1986, *Science* 233, 545-548--

Page 61: line 21;

In each instance of its use, as listed below, delete the citation "II-30" and insert --Mansour, S. L. and Martin, G. R., 1988, *EMBO J.* 1, 2035-2041--

Page 61: line 21;

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Page 17

In each instance of its use, as listed below, delete the citation "II-31" and insert --Amman, E. and Brosius, J., 1985, *Gene* 40, 183--

Page 26: line 18;

Page 55, line 2;

Page 65, line 11;

In each instance of its use, as listed below, delete the citation "II-32" and insert --Sakai, R. K., Scharf, S., Faloona, F., Mullis, K.B., Norn, G.T., Erlich, H.A. and Arnheim, N., 1985, *Science* 230, 1350-1354--

Page 55, line 7;

Page 65, line 15;

In each instance of its use, as listed below, delete the citation "II-33" and insert --Beckman, P.M., Betsholtz, C. Heldin, C-H., Westermarck, B. DiMarco, E., DiFiore, P.P., Robbins, K.C. and Aaronson, S. A., 1988, *Science* 241, 1346-1349--

Page 29: line 14 (incorrectly cited as II-32);

IN THE FIGURE LEGENDS AND TABLES

Page 89, Figure I-1, line 4: after "from", insert --five--

Page 91, Figure I-2, line 3: delete "0-6M", insert --0.6M--

Page 93, Figure I-4, line 12: triangular and square symbols
should be open (not closed)

Page 94, Figure I-5, line 13: delete "e) EGF + insulin" and
insert --e) EGF and dialyzed fetal calf serum (final
concentration, 10%); f) KGF and EGF; g) KGF and insulin; h) EGF
and insulin--

Page 95, Table II-1: column headings are reversed, i.e.,
delete " + - + -",
insert -- - + - + --

Page 99, Figure II-1, line 11: delete "and the open
region of the mature protein"

Page 99, Figure II-1, line 15: delete "right", insert --
left--

Page 99, Figure II-1, line 24: delete "lane d",
insert --lanes b and d--

Page 103, Figure II-3, lines 13-14: delete "647bp *EcoRI*
fragment from the 5' end", insert --*Bam*HI/*Bcl*I fragment
containing the majority--

Page 103, Figure II-3, line 18: after "cells", insert --
(B5/589); immortalized bronchial epithelial cells--

Page 103, Figure II-3, line 21: delete "AG1523", insert--
(AG1523)--

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Page 19

Page 103, Figure II-3, line 21: delete "AG1523", insert--
(AG1523)--

Page 75, line 22 through page 79, end, delete entire section
entitled "REFERENCES FOR EXPERIMENTAL SECTION II".


REMARKS

Consideration and allowance of the above-referenced
application, as amended, are respectfully requested.

The claims and specification have been amended to correct
various factual and typographical errors noted by the applicants
in reviewing the application prior to signature of the
Declaration.

The specification has also been amended to present the
citations of published works in the more customary style, namely
by incorporation directly into the text where cited.

Respectfully submitted,
CUSHMAN, DARBY & CUSHMAN

By 
Paul N. Kokulis
Reg. No. 16,773

PNK/PCK

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